Inadequately Explained Chronic Dry Eye Symptoms and Corneal Pain: New Insights and Concepts

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Abstract

We argue that inadequately explained chronic dry eye-like symptoms reflect corneal hypersensitivity to tear evaporation (evaporative hyperalgesia) and those associated with the spectrum of disorders currently labeled as dry eye disease are consequences of neuropathic disorders of the corneal trigeminal nociceptive pathways in which clinical manifestations are determined by the location and downstream effects of its dysfunctional elements.
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1. Introduction

Dry eye symptoms represent a specific type of corneal pain [1] characterized by their exacerbation in environments that accelerate tear evaporation and mitigation in those that suppress it, and by treatments that increase the robustness of the tear films. Dry eye disease (DED) is traditionally described as **Aqueous Deficient** defined by symptoms consistent with the signs of ocular surface desiccation and/or **Evaporative**, a much larger group characterized by symptoms disproportionately greater than those reflected by external ocular signs. Evaporative DED has been attributed to chronic Meibomian gland dysfunction (MGD) and the consequent attrition of the oil constituents of the tear film surface that normally serve to slow its evaporation. However, these paradigms fail to explain why levels of tear metrics and Meibomian gland function associated with chronic dry eye symptoms (CDES) in some patients are asymptomatic in others. We suggest that the theoretical disease model should be modified to accommodate this finding.

2. Dry eye symptoms

2.1 Background:

Sensory nerve injury triggers a cascade of events responsible for symptoms of hyperalgesia (increased sensitivity and responsiveness to noxious or near-noxious thermal, chemical and/or mechanical stimuli), allodynia (pain triggered by normally non-noxious stimuli) and spontaneous pain. Although pain evolved as a protective physiological warning of impending or actual tissue damage, it becomes a disease when it remains active long after its trigger has been withdrawn and the injured tissues have healed [2]. The definition of neuropathic pain is “**pain arising as a direct consequence of a lesion or disease affecting the somatosensory system**” [3]. Like somatic pain in other body parts, corneal neuropathic pain (CNP) can be initiated by damaged corneal nerves, the cell bodies of which reside in the trigeminal ganglion [4]. We posit that inadequately explained chronic dry eye symptoms represent neuropathic pain.

2.2. Transient Receptor Potential (TRP) Channels, Corneal Pain and Tear Regulation

The transducers of transient Receptor Potential cation channel subfamily M, member 8 (TRPM8) embedded in the neural sheaths of corneal nociceptors are designed to be activated by suprathreshold rates of cooling of their microenvironments, such as caused by evaporation [5, 6].
As tear films undergo evaporative thinning their thermal insulating effectiveness for the corneal surface diminishes and when the activation threshold of their cold transducers are breached, the lacrimal functional loop is activated and the tear layer thickness restored thereby silencing the alarm. Although this normally occurs at an unconscious level, an inadequate tear release response leads to an escalation of the alarm which is experienced as dry eye pain.

2.3. Nociceptors and Peripheral Sensitization
The sensitivity of the tear film monitoring alarm system is determined by the activation thresholds of its nociceptor. When their sensitivity is increased (and activation thresholds fall), the thickness of the overlying tear layer required to avoid triggering the alarm is also increased. In other words, sensitized corneas need thicker tear films than non-sensitized corneas to avoid feeling dry.

2.31. Proinflammatory Cytokines
Proinflammatory cytokines sensitizers released during inflammation are classic nociceptor sensitizers and induce hyperalgesia by lowering the activation thresholds of nociceptors to noxious stimuli [7]. Because the integrity of the optical tear layer tear is essential for functional vision it can be argued that the need to preserve it in the face of the threat of ongoing evaporation drove the evolution of the corneal pain system powered by the highest density of low threshold nociceptors in the human body. That many are uniquely tuned to tear evaporation explains their activation is interpreted as a threat of corneal surface drying. The presence of increased levels of proinflammatory cytokines in tears of eyes with signs of chronic corneal surface desiccation [8] and in those of patients diagnosed with evaporative DED [9] are consistent with the presence of chronic dry eye symptoms (CDES) due to corneal nociceptor sensitization).

Although hyperosmolar tears is a known cause of corneal inflammation [10], it is not a constant finding in non-desiccating dry eyes [11] despite elevated levels of cytokines. What is the source of the inflammation? We propose neuroinflammation [12] as a likely candidate. Considering the exceptionally high nociceptor density in the subbasal plexus, their intense prolonged activity may be capable of maintain a chronic state of peripheral sensitization.

2.32 Disinhibition of Inflammatory Sensitization?
Hyperalgesic priming, a phenomenon characterized by hypersensitivity to ambient proinflammatory cytokines [13], suggests that the degree to which nociceptor are sensitized can vary between individuals. The activity of ATP-sensitive potassium channel (K<sub>ATP</sub>) family has been shown to inhibit nociceptor sensitization [14] and might theoretically play a role in determining the intensity of the sensitizing response. However, its possible role in hyperalgesic priming and unexplained CDES has yet to be determined.

2.4. The scleral Lens Device: a Diagnostic Tool for Corneal Evaporative Hyperalgesia.
Because non-fenestrated scleral lenses instantly and completely block corneal surface evaporation on their insertion, symptoms that are suppressed are revealed as those of CEH. Moreover, by maintaining an optimal hydrating environment for the corneal surface and protecting it from friction normally generated by blinking (thus avoiding the activation of sensitized low threshold C-mechanoreceptors [15]), those symptoms of corneal pain experienced while they are worn are, by exclusion, spontaneous (the exception being chemical hyperalgesia, since the polymer from which this device is fabricated is permeable to fumes).

### 3 Corneal Neuropathic Pain Syndromes

#### 3.1 Age-Related Dry Eye Disease
The combination of depressed corneal tactile sensitivity (due to nerve fiber attrition [16]) and corneal evaporative hyperalgesia is the hallmark of age-related dry eye disease (ARDED). This is also consistent with the findings that although the overall activity of skin C-fibers in healthy elderly subjects is reduced, that of the surviving nerves was increased [17], reflecting hyperalgesia. In view of the far greater density of corneal nociceptors, the intensity of symptoms of (evaporative) hyperalgesia associated with corneal denervation hyper sensitivity would be expected to be far greater than that of skin. In this context, it seems plausible to consider ARDED a degenerative neuropathy. Moreover, the amplifying effects of aging on central pain-modulating processing [18] may also play a role in exacerbating symptoms of ARDED.

#### 3.2 Non Age-related Chronic Dry Eye Disease
Unexplained CDES are not limited to the elderly. A study of office workers experiencing similar symptoms [19] describes associated corneal features that differ from those associated with
ARDDED, including normal tear volumes and epithelial cell and nerve fiber densities [16]. The underlying pathogenetic mechanisms are unknown.

3.3 CDES following Corneal Injury:

In addition to inflammatory-driven hyperalgesia, pain following nerve trauma can also be triggered by hypersensitive ectopic pain-generators embedded in the neural sheaths of regenerating nociceptor fiber terminals [20]. Although some are known to discharge spontaneously [21], our informal observations that corneal symptoms are suppressed by scleral lens wear suggest that symptoms of CDES experienced in the months following LASIK/PRK are those of corneal evaporative hyperalgesia (CEH). Although they typically resolve within several months, CEH can persist as long as a year [22]. In some patients they can persist for much longer periods in which case it has become a neuropathic disease. (See CHRONIC EYE PAIN FOLLOWING LASIK AND PRK Rosenthal/Wu published on this website.)

3.4 Soft Contact Lens Intolerance

Although it is the leading cause of discontinued soft contact lens wear [23], the pathogenetic mechanisms of acquired soft contact lens intolerance remain a mystery. The comorbid presence of subclinical inflammation suggested by increased levels of proinflammatory cytokines found in the tears of these patients [24] and which are markers for hyperalgesia could be generated by the trauma cause by the enhanced transmission of blink-generated shearing forces to the corneal surface through partially dehydrated adherent soft contact lenses. We propose that the subclinical inflammation induced by this repeated trauma may induce sensitization of mechano-sensitive corneal nociceptors that once primed, are more easily reactivated. This hypothesis might also explain why symptoms of intolerance typically return rapidly after contact lens wear is resumed following long periods of discontinued contact lens wear.

4.0 Centralized Corneal Neuropathic Pain (CCNP)

Over the course of 5 years we examined 199 patients with corneal neuropathic pain who fit the criteria of CCNP (defined below). Laser scanning in vivo confocal microscopy (IVCM) of corneas was performed in all cases.

4.1 Peripheral Corneal Nerve Injury can trigger CCNP
Peripheral nerve injury injuries trigger changes in the structure, chemistry and function of the nociceptive elements in the dorsal horn [25] (and presumably trigeminal brainstem) and more rostral subcortical and cortical brain regions [26]. These include modifications of sensory pain states (e.g., hyperalgesia, allodynia), affect (e.g., mood) [27] and changes in cognition [28]. Ascending pain signals are amplified in the brain circuitry by an activity-driven system that incorporates feed-forward/back mechanisms. Known as central sensitization, this phenomenon is largely responsible for the unique behavior of pain to increase in intensity during the application of a constant noxious stimulus in contrast to all other sensory systems that respond by adaptation.) Central sensitization is regulated by an inhibitory feed-back system that limits central pain signal amplification and extinguishes its activity when incoming increased pain traffic ceases. However, intense sustained activity can ultimately entrench the changes in connectivity through maladaptive plasticity [29] which alters the balance of pain signal facilitation and inhibition in favor of the latter [30, 31]. Because the level of homeostatic level of synaptic excitability in the central nociceptive pathways is moved closer to the pain activation thresholds during the state of disinhibition they are more apt to be activated by normally subthreshold afferent noxious stimuli (hyperalgesia) and discharge spontaneously (spontaneous pain). In other words, symptoms of centralized pain are expressed through neurological mechanisms remote from its origins in the form of projected (phantom) pain. [32, 33]. Because the trigeminal nuclei in the brainstem serve as the principal center for processing/modulating and integrating corneal pain signals [34] and controlling the wetness of the corneal surface [35, 36], it may be possible for dysfunctional changes in this area of the brain to impact both functions.

The quality of spontaneous corneal pain typically differs from that of peripheral hyperalgesia in being commonly described as burning hot, sharp, cutting, needle-like, pressure/aching and/or by other descriptors not normally associated with CEH. Moreover, projected opthalmic pain can also be associated with headaches and painful sensations experienced in the orbits, ears, face, jaws and teeth. A few patients in our cohort experienced alldynia (perception of non-noxious stimuli as painful) in skin innervated by the ophthalmic branch of the trigeminal nerve. Strikingly, some reported that topical corneal anesthesia failed to either completely or partially mitigate their eye including some with normal appearing confocal microscope images of their corneal subbasal plexus (personal observations) suggesting that the pain was generated central to the trigeminal ganglion. On the other hand, our informal observations suggest that this proof of the
presence of projected corneal pain as divorced from peripheral nociception may not be apparent in the earlier stages of peripherally triggered centralized pain.

Although the wearing comfort of well-fitted scleral lenses is typically reported as excellent, a strikingly high number of these patients were unable to tolerate them. The clinical patterns of the pain reported by these patients appear to be consistent with centralized pain. This association has been previously reported [37]. We have observed this during patients’ initial fitting or months to years after the devices had been worn successfully. This complication was sometimes associated with an unusually painful response to the application of Schirmer’s test strips.

4.2. Photoallodynia

Photosensitivity was described as a significantly disabling symptom in many of our patients. Strikingly, it differed from that associated with corneal damage in many ways, including the absence of signs and symptoms associated with inflammation of the anterior segment of the involved eyes. The absence of miotic pupils, ciliary flush and the typical aching sensation triggered by light exposure was notable as was the failure of cycloplegia to mitigate symptoms. Although sometimes associated with disproportionately modest signs of corneal epithelial desiccation, we argue that it is best classified as a form of alldynia; hence our use of the neogilistic term photoallodynia. This is further supported by the descriptions by many of these patients that exposure to light triggered an exacerbation of their corneal neuropathic pain [38]. Yet another unique feature found in many of these patients is their awareness that lights of fluorescent and metal halide fixtures and of computer screens are more painful compared to incandescent light. In our effort to reconcile these findings we speculate that although photoalldynia is associated with the activation of corneal-trigeminal pathways similar to that of anterior segment inflammation [39], photoalldynia is initiated in and sustained by neuropathic disorders involving the relevant central pain modulating centers such as those in the brainstem [36]. Symptoms of photoalldynia appear to be similar to those described by migrainous patients [40] although, to our knowledge, the amplified effects of lights with high frequency flicker has not been reported in the latter disorder.

Photophobia following corneal damage [41] is characterized by the activation of corneal-trigeminal pathway [39]. Disabling photosensitivity was commonly reported by our patients, and
similar to corneal neuropathic pain, was characterized by the disparity of symptoms and signs (personal observations). Moreover, unlike traditional photophobia which is described as an aching sensation (consistent with ciliary body spasm), symptoms of photoallogdynia are typically described as the intensification of CCNP pain [38]. This difference is also highlighted by the apparent failure of cycloplegia to mitigate this response (personal observations). Especially notable are reports that the pain is especially intensified by exposure to the lights of fluorescent and metal halide fixtures and computer terminals in comparison to incandescent lights.

We believe that these findings support considering photoallogdynia as a surrogate of CCNP and a consequence of neuropathic central sensitization involving the trigeminal brain stem [36]. Symptoms of neuropathic photosensitivity previously described as photoallogdynia [38] appear to be similar to those described by migrainous patients [40] although the amplified effects of lights characterized by high frequency flicker has not been reported in this cohort to our knowledge.

4.3. Centralized Corneal Neuropathic Pain following Laser Keratorefractive Surgery

In a cohort of patients (n=21) that developed putative CCNP following laser keratorefractive procedures in which its duration had ranged from 2 to 15 years at the time of the initial consultation, 81% reported that photophobia was a significant component of their symptoms [see case report series published on this website]. Strikingly, the majority (62%) described an asymptomatic postoperative period prior to the onset of CCNP that lasted years in some that is similar to reports of somatic neuropathic pain that followed surgery involving other body parts [42]. If confirmed, it suggests that some of the currently asymptomatic post keratorefractive surgery patients may continue to be at risk for developing CCNP.

4.4. Chronic Corneal Pain Associated with Multisystem Disorders

Patients with Sjogren’s syndrome (SS) are the poster child for desiccating dry eye disease. Nevertheless, our informal observations are consistent with those reported in a study that failed to show a significant difference between the tear metrics of SS patients and those of an age-matched healthy population [43]. How can these findings be reconciled with historical belief? While following the course of the disease in SS patients referred for treatment of refractory DES we observed that some patients whose ocular surfaces were normal to slitlamp examination including tear films subsequently developed severe significant deficiency, thereby giving credence to the possibility that the initial symptoms were neuropathic while the consequences of the
attrition of functional lacrimal acini occurred later in their disease. The known association of SS and an increased incidence of peripheral neuropathy [44] appears to strengthen this hypothesis.

A number of patients in our cohort who carried a diagnosis of fibromyalgia were similarly characterized by a disparity between symptoms and tear metrics as had been previously reported [45]. The diversity of diseases associated with CCNP suggests the possibility that they might share an underlying vulnerability to is complication. Reports of the presence of mitochondrial dysfunction in patients with SS [46] and fibromyalgia [47] and in a murine model neuropathic pain [48] suggests a possible link that may be worth exploring.

5. Corneal Neuropathic Pain: an Overview

A validated mechanism-based classification of neuropathic corneal pain could offer a helpful platform for extending our knowledge of its pathophysiological mechanisms and open new pathways for exploring the development of effective treatments [49]. The human cornea has unique properties that make it an ideal substrate for studying nociceptive disorders including unequaled density of nociceptors, relatively discrete central pain signaling pathways and the ability to induce temporary and reversible corneal anesthesia conveniently, safely and non-invasively. Moreover, the accessibility of corneal axons to in vivo confocal microscope imaging is a powerful diagnostic and research tool.

5.1. A Proposed Classification for Corneal Neuropathic Pain

We chose the acronym KN for Keratoneuralgia, a term suggested by Dan Jones MD (personal communications). KN-A refers to CNP triggered by noxious or normally non-noxious corneal stimuli sustained by dysfunctional nociceptors and/or primary nerve fibers, whereas KN-B refers to corneal pain incorporating a centralized component. The growing appreciation of the contribution of malfunctioning elements in the central nociceptive pain signaling pathways in the generation and the maintenance of certain forms of corneal neuropathic pain warrants it being positioned as the central feature of the second major category in our classification. Nevertheless, both subgroups may be present simultaneously and have interacting consequences.

Keratoneuralgia-Type A (KN-A) includes 5 subcategories: KN-A1 (desiccating dry eye), KN-A-2 (ARDED), KN-A-3 (non-ARDED), KN-A-4 (pathologically persistent corneal nerve fiber
regeneration) and KN-A-5 (active corneal axonopathy associated with more widespread sensory disorders).

KN-A1 defines corneal neuropathy in which the intensity of symptoms of CEH and photoallodynia mirror the signs of corneal desiccation. Although not known to be inherently self-sustaining, its promotion of the release of sensitizing cytokines in the presence of existing hyperactive nociceptive activity associated with primary corneal neuropathies may have synergistic consequences.

KN-A2: This subgroup is characterized by symptoms of CEH associated with aging peripheral corneal nociceptive systems that exhibit the features consistent with denervation hypersensitization such as symptoms of corneal evaporative hyperalgesia and attrition of primary nerve fibers.

KN-3: Although symptoms KN-A3 are indistinguishable from those of KN-A2, this subcategory differs in its younger age, normal tear metrics and corneal nerve fiber densities (other than their increased varicosities). Its identification as a cohort is recent, having been described by in a single study. Its possible evolution to centralized pain is unknown.

KN-A4: Like those of the first 3 subgroups its, symptoms are characteristic of CEH. However, this disease is defined by the pathological persistence of the healing phenotype of corneal nerves following axotomy long after the corneal tissue has otherwise healed. KN-A4 can trigger CCNP (personal observations).

KN-A5 is identical to KN-A3 with the exception of the lack of a known noxious corneal trigger. It can be associated with small fiber neuropathy and central neurological disorders such as focal dystonias (blepharospasm [50]) and, like KN-A4, typically evolves to KN-B (personal observations).

Keratoneuralgia- Type B (KN-B): This category refers to CCNP. Although we believe that spontaneous referred pain is diagnostic of this category, its symptoms may also include or be limited to those of corneal hyperalgesia. Symptoms of the latter typically differ from those associated with KN-A in having higher intensities and the possible co-presence of chemical and cold corneal hyperalgesia. The presence of mechanical hyperalgesia may also signal its presence as intolerance to scleral wear. Photoallodynia is a common (and sometimes dominant) symptom
that we believe is diagnostic of KN-B. Symptoms are pleomorphic and often unstable and unpredictable. Although our current knowledge of CCNP may be insufficient to classify this cohort with a high degree of confidence, there may be some value in attempting this in order to bring order to our informal observations. In some cases it can evolve from KN-A3 and KN-A4 or be associated with other neurological and multisystem disorders. On the other hand, centralized corneal pain may appear as a seemingly isolated disease.

KN-B1 subgroup defines CCNP in which symptoms are limited to those of corneal hyperalgesia that differ from those of KN-A2 by their greater intensities and the possible presence of chemical, mechanical and cold hyperalgesia.

KN-B2 is identified by spontaneous pain having a range of sensations that can project to trigeminal territories beyond the cornea.

6. Assessment of Corneal Neuropathic Pain

6.1 History

Onset and trajectory: This information can provide important clues for identifying its principal components. For example, a history of a preceding noxious corneal event and the time frame between the triggering event and the onset of chronic corneal pain can be helpful in classifying the disease. Moreover, its trajectory is helpful for estimating the prognosis.

Symptoms: A detailed description of each painful element (more than one type of pain is typically present) is central to establishing the classification of the neuropathic pain syndrome and for designing individual therapeutic strategies. This exercise requires the posing of thoughtful questions and careful listening after first establishing a mutually agreed-to vocabulary for its descriptors. Each pain element should be categorized as being spontaneous or provoked. Symptoms of CEH should be highlighted as they are the most amenable to palliative treatments. Moreover, certain pain characteristic such as their radiation, sharp, aching, severe burning, chemical and cold hyperalgesia appear to be characteristic of centralized pain.

Comorbid Extra-corneal Pain in the Trigeminal Receptive Field: Centralized pain can spread to involve head, orbits, ears, face, jaws and throat. Amplification and distortion of other sensory inputs such as sound (including tinnitus), smell, taste and light (photoalodyniam) are less common.
**General health:** Symptoms consistent with diseases known to be associated with a higher incidence of neuropathic pain (such as the poorly understood multisystem disorders) are especially important to identify. These include chronic fatigue, gastrointestinal complaints, chemical hypersensitivities, chronic pelvic pain, vulvodynia and muscle and joint pain. A list of past and current medications including their effectiveness and side-effects should be recorded. Sensory anomalies of receptive fields beyond the trigeminal nerve may reflect the presence of more widespread neuropathies or other neurological diseases.

Because of the bidirectional effects of emotional states such as depression, post-traumatic stress disorder and catastrophization on the clinical expressions of neuropathic pain [51] [52] [53], their status should be targeted as possible disorders for treatment.

**Family history:** The health history of 1st degree family members can be helpful for assessing patients’ risks for developing neuropathic disease. Few genetic studies on dry eye have been reported but variants of genes, such as mucin MUC1 may be altered in dry eye [54]. However, others associated with painful neuropathies or pain predisposition have not yet been evaluated.

6.2. Examination

In addition to the standard eye examination with attention focused the external ocular surfaces it is important to assess the responses of patients’ symptoms to corneal anesthesia in each eye separately. Moreover, the intensity of the pain provoked by the anesthetic drops themselves immediately on their instillation can be helpful in assessing the presence of corneal chemical hyperalgesia because an unusually painful response points to centralized pain. The maximum degree of pain suppression should be recorded as ‘none’, ‘incomplete’ or ‘total’. Reports of complete pain suppression should be verified, especially if the intensity of the pain is high, since dramatic relief can overshadow persistent but barely perceptible levels that are no less significant.

Measurements of corneal tactile sensitivity (Cochet-Bonnet esthesiometry) are especially important if laser scanning confocal microscopy is unavailable since depressed values indicate the presence of damaged corneal nerves or their reduced densities. However, esthesiometry is not a substitute for images provided by laser scanning confocal microscopy images of the corneal subbasal plexus. The presence of hyperalgesia, allodynia and amplified temporal summation [55] of the skin innervated by the trigeminal nerve supports the presence of centralized pain.
7. Current Therapeutic Options

Symptoms of CEH is treated empirically with palliative measures directed to enhancing the robustness and durability of the tear film. These include the use of artificial tears, improving Meibomian gland productivity and reducing/suppressing tear evaporation. However, if they are inadequate and the level of disability warrants a trial of topical steroids, the use of non-preserved topical dexamethasone 0.01% should be considered [56]. Topical autologous serum drops has been reported to mitigate symptoms and promote corneal nerve regeneration in some patients [57, 58] and a recent study described a reduction in corneal vital dye corneal staining and symptoms following the use of an investigational topical mucin secretagogue [59].

The value of systemic analgesics as first line treatment is limited by their relative ineffectiveness and disabling side effects including drowsiness, loss of coordination and compromised cognition [60, 61]. The most commonly used classes of oral neuropathic analgesics prescribed for these disorders are the gabapentiods (gabapentin and pregabalin) and antidepressants (duloxetine and nortriptyline). Drug combinations can sometimes be more effective than single medications [62]. The chronic use of opioids by other than terminally ill patients should be avoided if possible because, in addition to risks of tolerance, addiction and increased sensitivity to emotional distress [63], it can result in the intensification of pain symptoms [64, 65]. Moreover, their long-term efficacy (>8 weeks) has not been demonstrated [66]. Effective treatment of comorbid depression and anxiety with antipsychotic medications can be helpful in reducing pain intensity [67].

The lack of effective treatments for centralized pain highlights the importance of its prevention. The period of transition from acute to chronic pain following corneal nerve injury may represent a window of opportunity for interventions potentially capable of reducing the potential development of neuropathic pain through the use of preemptive analgesics [68], aggressive treatment of acute pain [69, 70] and perhaps therapeutic interventions that may offer the possibility of accelerating corneal nerve healing [71].
8. Conclusions

The striking ability of scleral lenses to completely suppress chronic dry eye symptoms regardless of existing tear metrics validates the findings of corneal neurophysiologists who mapped out the mechanistic framework of the tear film thickness alarm system. We argue that the initial phase of DED is driven by malfunctioning hypersensitive sensors that require thicker-than-normal tear films to maintain their silence. We further postulate that these neuropathic changes compromise the secretory activity of the functional lacrimal loop over time, thereby further increasing symptom. Although corneal inflammation provoked by tear insufficiency/hyperosmolarity plays a central role in increasing nociceptor sensitization, the inconsistent relationships between symptoms and tear metrics and between tear osmolarity and Meibomian gland function imply the presence of another, previously unreported source of inflammation that we suggest is neuroinflammation generated by the intense ongoing nociceptive activity provoked by their sensitization. Moreover, we argue that inadequately explained CDES and centralized spontaneous pain are symptoms of a spectrum of neuropathic disorders involving the peripheral and/or central corneal nociceptive systems. The diversity of non-ocular medical disorders that share these symptoms raises the possible existence of shared pathogenetic pathways.

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